

The Epidemiology of Fluoroquinolone-Resistant *Neisseria gonorrhoeae* in Hawaii, 2001

Lori M. Newman,¹ Susan A. Wang,¹ Roy G. Ohye,² Norman O'Connor,³ Maria V. Lee,² and Hillard S. Weinstock¹

¹Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; and ²Hawaii State Department of Health, Honolulu, and ³State of Hawaii Department of Health Laboratories Division, Pearl City, Hawaii

Increases in the number of infections with fluoroquinolone-resistant *Neisseria gonorrhoeae* in Asia and the United States threaten the efficacy of fluoroquinolones as inexpensive, single-dose, orally administered treatments for gonorrhea. This report describes the findings of a field investigation of an increase in the number of infections with ciprofloxacin-resistant *N. gonorrhoeae* (CipRGC) in Hawaii in 2001. We conducted a case review of 53 patients with CipRGC, who constituted 20% of the 267 patients with cultures positive for *N. gonorrhoeae* during this period. Nearly one-half of patients with CipRGC were seen by clinicians in private practice, one-third were seen by clinicians at a sexually transmitted diseases (STD) clinic, and only 2% were seen by clinicians in the military. Among the 117 patients with culture-confirmed gonorrhea who attended the public STD clinic, we found a prevalence of infection with CipRGC of 17%. The demographic and clinical characteristics of patients with CipRGC were similar to those of patients with gonorrhea that was not resistant to ciprofloxacin, suggesting that fluoroquinolone-resistant gonorrhea has become endemic in Hawaii.

A significant challenge in the control of infections caused by *Neisseria gonorrhoeae* has been the ease with which *N. gonorrhoeae* develops resistance to commonly used antimicrobial therapies [1]. Through chromosomal- and plasmid-mediated resistance mechanisms, *N. gonorrhoeae* has demonstrated resistance to nearly all classes of drugs used to treat gonorrhea [2]. Soon after the widespread emergence of penicillin and tetracycline resistance in the 1980s, fluoroquinolones became available as single-dose, orally administered treatments for gonorrhea [3]. Fluoroquinolones (e.g., ciprofloxacin, ofloxacin, and levofloxacin) and cephalosporins (ceftriaxone and cefixime) are currently the primary antimicrobials recommended by the Centers for Disease Control and Prevention (CDC; Atlanta, GA) for the treatment of gonorrhea [4]. In 2001, fluoroquinolones

were used to treat 39% of the patients with gonococcal infection who participated in the Gonococcal Isolate Surveillance Project (GISP) [5].

The prevalence of gonococcal resistance to fluoroquinolones has increased in the United States and several other countries, presenting a threat to the effectiveness of fluoroquinolones for the treatment of gonorrhea [5, 6]. Surveillance programs in Asia have demonstrated a prevalence of fluoroquinolone-resistant *N. gonorrhoeae* of >50% in some countries [7]. GISP, established in 1986, is a sentinel surveillance system that monitors trends in the antimicrobial susceptibility of *N. gonorrhoeae* by testing urethral specimens obtained from male patients at sexually transmitted diseases (STD) clinics in ~25 US cities. In 1991, GISP identified the first fluoroquinolone-resistant isolate in the United States in Honolulu, Hawaii. Since 1991, fluoroquinolone-resistant gonococcal isolates have been identified throughout the United States, but the highest prevalence has consistently been seen in Honolulu [5].

Unlike other states, in Hawaii, the Department of Health Laboratories Division (HDHLD) has routinely performed antimicrobial susceptibility testing on all *N. gonorrhoeae* isolates since 1993, and a large proportion

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Reprints or correspondence: Dr. Lori Newman, Mailstop E-02, 1600 Clifton Rd., Atlanta, GA 30333 (len4@cdc.gov).

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of reported gonorrhea cases are diagnosed on the basis of culture results. In 2001, for example, antimicrobial susceptibility testing was performed on *N. gonorrhoeae* isolates in 267 (44%) of the 605 reported cases of gonorrhea. Furthermore, the Hawaii State Health Department (HSHD) has actively tried to interview all patients identified with fluoroquinolone-resistant *N. gonorrhoeae* and maintains a database of patient information.

In November 2001, the HSHD notified CDC of the recent increase in the number of fluoroquinolone-resistant gonococcal infections. In January 2002, CDC sent a team to investigate this increase and to assist the HSHD in developing appropriate control interventions. The analyses presented here are a summary of the findings from this field investigation.

PATIENTS AND METHODS

To identify the extent of the increase in the number of ciprofloxacin-resistant *N. gonorrhoeae* (CipRGC) infections and the demographic and clinical characteristics of the infected patients, a case ascertainment of CipRGC infection was performed, as well as a cross-sectional survey of public STD clinic records of patients who had received a diagnosis of gonorrhea.

Case review of CipRGC infection. HDHLD received gonococcal cultures from the HSHD STD clinic, as well as from a variety of other clinical settings. We performed a retrospective record review of all patients with cultures positive for *N. gonorrhoeae* strains that were determined by the HDHLD to be resistant to ciprofloxacin on the basis of 1998 NCCLS criteria [8] and that were received by the laboratory during the period of 1 January 2001 through 31 December 2001. NCCLS defines ciprofloxacin resistance as an MIC of ≥ 1.0 $\mu\text{g/mL}$ (by agar dilution) or a disk-diffusion zone size of ≤ 27 mm.

Data on patients in the case review were extracted from the existing surveillance database, as well as from interview and clinical records available at the HSHD STD clinic. Information extracted from the records included basic demographic information, clinician type, reported sexual behavior, recent travel by the patient or the patient's sex partner(s), military employment or report of recent sexual contact with military personnel, being a sex worker or report of recent sexual contact with a sex worker, current or recent antibiotic use, current symptoms, test results for chlamydial infection, and antibiotic therapy received for gonorrhea. The term "recent" was used when the time frame varied between data sources (usually 30–60 days) or was not clearly defined.

STD clinic cross-sectional survey. We performed a retrospective cross-sectional survey involving patients who received a diagnosis of gonorrhea at the HSHD STD clinic from 1 January 2001 through 31 December 2001. Patients with CipRGC infections were compared with patients with *N. gon-*

orrhoeae infections that were not ciprofloxacin resistant (non-CipRGC). We defined patients with CipRGC infection as patients seen at the STD clinic during this period from whom *N. gonorrhoeae* resistant to ciprofloxacin (as determined by the HDHLD on the basis of 1998 NCCLS criteria) was recovered from any anatomic site. We defined patients with non-CipRGC infection as patients seen at the STD clinic during this period from whom *N. gonorrhoeae* susceptible (CipSGC) or intermediately resistant (CipIGC) to ciprofloxacin was recovered from any anatomic site. For *N. gonorrhoeae*, NCCLS defines intermediate resistance to ciprofloxacin as an MIC of 0.125–0.50 $\mu\text{g/mL}$ (by agar dilution) or a disk-diffusion zone size of 28–35 mm, and ciprofloxacin susceptibility as an MIC of ≤ 0.06 $\mu\text{g/mL}$ (by agar dilution) or a disk-diffusion zone size of >35 mm.

Data were extracted from clinical records, interview records, and laboratory reports. Patient information similar to that used in the case review was extracted from these records. Data were entered into EpiInfo, version 6.04d (CDC), for analysis. Data were described using prevalence ratios (PRs) and 95% CIs. PRs were chosen to describe these data because all of the individuals in the STD clinic population for whom cultures were positive for gonorrhea were included in the analysis. This activity underwent human subjects review at CDC and was determined to be a disease-control activity and not research.

RESULTS

Case review of CipRGC infection. In 2001, isolates from 53 (20%) of 267 patients with HDHLD gonococcal culture and susceptibility test results were positive for CipRGC. Nearly one-half of the patients infected with CipRGC were seen by clinicians in private practice, one-third were seen by clinicians at the STD clinic, and 2% were seen by clinicians in the military during this period (table 1).

Demographic and clinical characteristics of patients in the case review are summarized in table 1. History of travel to Asia or having had a sex partner with such history was reported by 26% of these patients. More than one-half of the patients infected with CipRGC were of Asian/Pacific Islander race. Few reported being a sex worker, having had sexual contact with a sex worker, being a member of the military, or having had sexual contact with military personnel. Information on the presence or absence of STD symptoms was available for ~60% of the patients, all of whom were symptomatic. Documentation of antimicrobial therapy was available for 47 patients (89%), of whom 5 had received inappropriate treatment with fluoroquinolones (4 were treated by clinicians in private practice, and 1 was treated by a clinician in the military). One of these 5 patients had documentation of subsequent re-treatment with appropriate antimicrobial therapy; it was unknown if the re-

Table 1. Demographic and clinical characteristics of 53 patients with ciprofloxacin-resistant *Neisseria gonorrhoeae* infection, Hawaii, 1 January 2001–31 December 2001.

Characteristic	Value
Female sex	23/53 (43)
Age, median years (range)	29 (15–67)
Race/ethnicity	
American Indian	1/53 (2)
Asian/Pacific Islander	28/53 (53)
Chinese	1/28 (4)
Filipino	8/28 (29)
Guamanian	1/28 (4)
Hawaiian	8/28 (29)
Japanese	3/28 (11)
Korean	1/28 (4)
Micronesian	2/28 (7)
Vietnamese	1/28 (4)
Unknown	3/28 (11)
Black	5/53 (9)
Hispanic	2/36 (6)
White	12/53 (23)
Other/unknown	7/53 (13)
Island of residence	
Hawaii	1/51 (2)
Maui	2/51 (4)
Oahu	48/51 (94)
Health care facility type	
Correctional facility	2/53 (4)
Emergency department/hospital	4/53 (8)
Family planning clinic	1/53 (2)
Military installation	1/53 (2)
Private clinic	25/53 (47)
STD clinic	20/53 (38)
Men who have sex with men	4/21 (19)
Recent sex partners, median no. (range)	1.0 (0–4)
Recent travel to Asia ^a	10/38 (26)
Sex worker ^a	5/32 (16)
Military employment ^a	6/32 (19)
Recent antibiotic use	5/34 (15)
Symptomatic	32/32 (100)
Fluoroquinolone use	5/47 (11)
Chlamydial coinfection	9/26 (35)

NOTE. Data are no. of patients/total no. of patients for whom data were available (%), unless otherwise indicated.

^a Patient and/or sexual partner of patient.

maining 4 patients were re-treated with appropriate antimicrobial therapy.

STD clinic cross-sectional survey. There were 117 patients with culture-confirmed diagnoses of gonorrhea who visited the STD clinic during the period of 1 January 2001 through 31

December 2001; 20 patients (17%) were infected with CipRGC, and 97 (83%) were infected with non-CipRGC (3 with CipIGC and 94 with CipSGC). Medical records were available for 116 of these patients. Demographic information was available in the surveillance database for all 117 patients, and risk factor information was available for 88 (75%).

Among patients with gonorrhea, the prevalence of CipRGC infection was significantly lower among men who reported sex with men than among men who reported sex only with women (1 [3%] of 29 vs. 12 [22%] of 55; $P = .03$). The prevalence of CipRGC infection was higher among patients with a history of recent travel to Asia or a sex partner with such history than among patients without such history or partners (4 [36%] of 11 vs. 15 [15%] of 102; $P = .07$), but the difference was not statistically significant. Among patients with gonorrhea, CipRGC prevalence was similar for Asian/Pacific Islanders and non-Asian/Pacific Islanders (10 [19%] of 54 vs. 10 [16%] of 63; $P = .70$) (table 2). The group of patients with CipRGC infection also did not differ significantly from the group with non-CipRGC infection according to sex, ethnicity, having recently had sexual contact with military personnel and/or sex workers, current or recent antibiotic use, and the presence of STD symptoms.

DISCUSSION

After identification of the first CipRGC isolate in Hawaii in 1991, the annual prevalence of CipRGC infection in Hawaii from 1993 through 1997 remained at or less than 1% (figure 1). In 1998, this rate increased to 6% [9] and, by 2001, had reached ~20%. The first epidemiologic description of fluoroquinolone-resistant gonococci in the United States—CipRGC isolates in 3 patients in Hawaii who had recently traveled to The Philippines—was published in 1994 [10]. An investigation in 1999 of patients infected with fluoroquinolone-resistant *N. gonorrhoeae* found that STD clinic patients infected with CipRGC or CipIGC were more likely to have recently traveled to Asia, to have had a sex partner with such history, or to be Filipino than were patients with CipSGC infection [11]. The 1999 report suggested that, through 1999, transmission of gonorrhea due to CipRGC was still occurring primarily in populations with an identifiable risk factor. However, because prevalence of CipRGC infection was high, the HSHD and CDC recommended in 2000 that fluoroquinolones should not be used to treat any patients with gonorrhea that was acquired in Hawaii [9].

Our analysis of STD clinic patients with gonorrhea demonstrated that the prevalence of CipRGC infection was high in all of the risk groups in the evaluation. Furthermore, data in our case review showed that the racial and ethnic distribution of patients infected with CipRGC was similar to that of the

Table 2. Prevalence of ciprofloxacin-resistant *Neisseria gonorrhoeae* (CipRGC) infection among 117 patients at a sexually transmitted diseases (STD) clinic, Hawaii, 2001.

Characteristic	Patients with CipRGC	Prevalence ratio (95% CI)	P
Sex		0.6 (0.3–1.5)	.29
Male	13/87 (15)		
Female	7/30 (23)		
Asian/Pacific Islander		1.2 (0.5–2.6)	.70
Yes	10/54 (19)		
No	10/63 (16)		
Hispanic		0.9 (0.2–3.3)	.83
Yes	2/13 (15)		
No	17/96 (18)		
Men who have sex with men		0.2 (0.02–1.2)	.03 ^a
Yes	1/29 (3)		
No	12/55 (22)		
Recent travel to Asia ^b		2.5 (1.0–6.2)	.07
Yes	4/11 (36)		
No	15/102 (15)		
Military employment ^b		0.3 (0.04–2.0)	.15
Yes	1/22 (5)		
No	11/67 (16)		
Sex worker ^b		2.0 (0.3–11.7)	.49
Yes	1/4 (25)		
No	10/78 (13)		
Recent antibiotic use		1.0 (0.1–6.8)	.99
Yes	1/8 (13)		
No	10/79 (13)		
STD symptoms		1.7 (0.4–6.6)	.44
Yes	18/97 (19)		
No	2/18 (11)		

NOTE. Data are no. of patients/total no. of patients for whom data were available (%).

^a Statistically significant.

^b Patient and/or sexual partner of patient.

general population [12]. The high prevalence of CipRGC infection in a wide variety of risk groups and an overall prevalence of CipRGC of 20% in 2001 suggest that CipRGC is endemic in Hawaii ~10 years after the initial identification.

Data from GISP showed an increase in the national prevalence of CipRGC isolates from 0.4% in 2000 to 0.7% in 2001. Although part of this national increase is attributable to increases in Honolulu (1 of 25 GISP sites), notable increases in the number of CipRGC isolates have also been seen in California sites [5, 13]. The presence in Hawaii of large numbers of US military personnel, Asian immigrants, and tourists from both the United States and Asia means that clinicians throughout the United States must be aware of the potential spread of CipRGC, because all 3 of these populations are highly mobile.

In response to the increased prevalence of CipRGC in several

areas [13], the CDC recommended that quinolones should not be used to treat gonococcal infections acquired in Asia, the Pacific Islands (including Hawaii), California, and other areas where there is increased prevalence of fluoroquinolone resistance [4]. Ceftriaxone, cefixime, or spectinomycin are the recommended treatment options in such clinical settings. (Manufacture of cefixime in the United States was discontinued in July 2002 [14]. A discussion of oral alternatives to cefixime for the treatment of gonorrhea is available at <http://www.cdc.gov/std>.) To select appropriate gonorrhea treatment for patients in the United States, it is crucial that clinicians ask patients with gonorrhea about their recent travel history, as well as that of their sex partners. Although fluoroquinolone use is inadvisable in some clinical settings, for many patients in the United States, fluoroquinolones remain an important gonorrhea treatment option.

The data from this study highlight the value of performing routine surveillance of gonococcal antimicrobial susceptibility. Such information is important in forming decisions about antimicrobial therapy for treating gonorrhea. Unfortunately, gonococcal antimicrobial susceptibility data are limited for US sites not participating in GISP. Antimicrobial susceptibility testing can be performed only on *N. gonorrhoeae* culture isolates, rather than on specimens obtained for nucleic acid amplification or nucleic acid hybridization testing. Owing to easier specimen collection and transport requirements, tests that do not involve culture have replaced gonococcal culture in many clinical settings. A national survey of public health laboratories and a few private laboratories found that, in 2000, only 18% of *N. gonorrhoeae* testing was done using culture methods, and only approximately one-third of the laboratories that used culture methods also performed antimicrobial susceptibility tests [15].

There were several important limitations to the data presented here. The vast majority of cases of gonorrhea in Hawaii are reported from Oahu, the most populous island, where Honolulu is located. Because of limited laboratory resources and the costs and difficulties associated with specimen transport, on other islands, gonorrhea may be treated empirically without testing or may be diagnosed without use of culture. Unpublished 2001 Hawaii surveillance data demonstrated that 2% of military patients, 44% of private patients, and 95% of STD clinic patients reported with gonorrhea had received their diagnosis on the basis of culture and antimicrobial-susceptibility test results. Patients seeking care from clinicians in the military or private practice were less likely to have received diagnoses on the basis of gonococcal culture results than were patients who sought care at the public STD clinic. Clinical information was not routinely collected for patients who did not attend the STD clinic, contributing to likely underrepresentation of the risk behavior of private and military patients in the case review of CipRGC infection. Reporting of gonorrhea cases in the

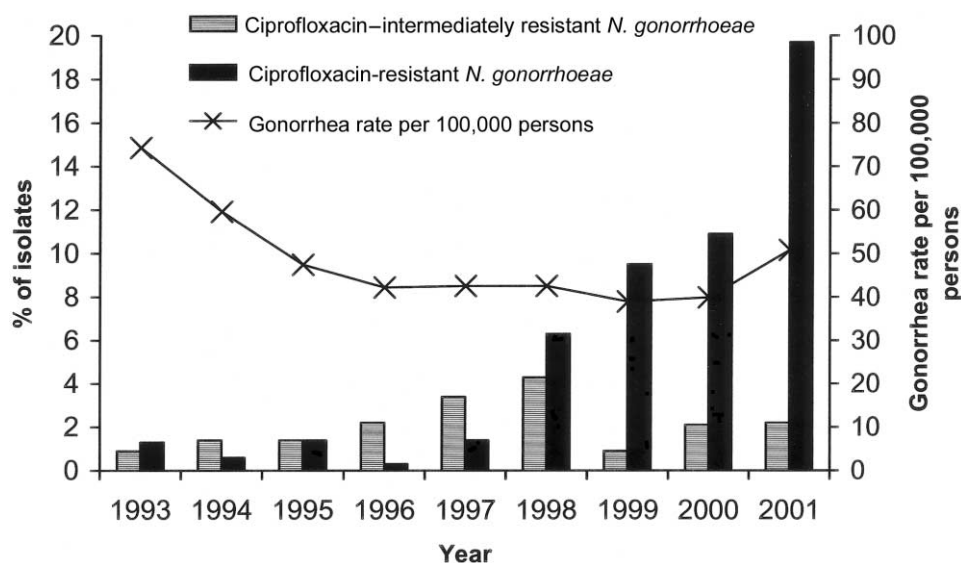


Figure 1. Rate of gonorrhea and the prevalence of infection with ciprofloxacin-resistant and -intermediately resistant *Neisseria gonorrhoeae* among patients with culture-confirmed gonorrhea, Hawaii, 1993–2001. *N. gonorrhoeae* resistance to ciprofloxacin is defined by NCCLS as an MIC of ≥ 1.0 $\mu\text{g/mL}$ (by agar dilution) or a disk-diffusion zone size of ≤ 27 mm, and intermediate resistance is defined as an MIC of 0.125–0.5 $\mu\text{g/mL}$ (by agar dilution) or a disk-diffusion zone size of 28–35 mm.

United States is estimated to identify only ~50% of all gonorrhea cases [16]. In addition to populations in which gonorrhea is underreported, several populations in Hawaii may be disproportionately underrepresented by the state gonorrhea surveillance system. Such populations include tourists who may be treated empirically because of difficulties in providing follow-up care, drug users who may not seek care, and immigrant women working in social venues who may avoid use of formal medical care because of language barriers or fear of disclosure of illegal immigrant status.

In response to increases in the number of cases of fluoroquinolone-resistant gonorrhea in 1999, the HSHD issued a medical alert in April 2000 advising clinicians to discontinue use of fluoroquinolones for the treatment of gonorrhea. In February 2002, HSHD issued a follow-up medical alert informing clinicians that the proportion of gonorrhea cases with fluoroquinolone resistance had further increased and re-emphasizing the importance of avoiding fluoroquinolones for the treatment of gonorrhea in Hawaii. In October 2002, HSHD hosted several days of training for local clinicians and community outreach workers in which STD prevention, diagnosis, and treatment was addressed. In November 2002, the increases were communicated to the national public health community via a report in the *Morbidity and Mortality Weekly Report* [13]. The HSHD has continued to gather information on patients with fluoroquinolone-resistant gonorrhea, to use culture to diagnose gonorrhea in patients visiting the public STD clinic, and to perform antimicrobial susceptibility tests on all gonococcal isolates.

It is clear that fluoroquinolone-resistant *N. gonorrhoeae* has become endemic in Hawaii ~10 years after its initial identification. It will be important to routinely monitor gonococcal antimicrobial susceptibility throughout the United States, because it is unclear how much longer fluoroquinolones will continue to be effective treatments for gonorrhea in other states.

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